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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02021837.6	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/10701	International filing date *(day/month/year)* 25.09.2003	Priority date *(day/month/year)* 27.09.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/47		
Applicant BIOMAY PRODUKTIONS- UND HANDELS-AKTIENGES... et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2004	07.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Sprinks, M Telephone No. +49 89 2399-7706

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10701

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Sequence listings part of the description, Pages

1-6 as originally filed

Claims, Numbers

1-15 received on 17.09.2004 with letter of 17.09.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

   see separate sheet

The following documents (D) are mentioned for the first time in this opinion/report; the numbering will be adhered to in the rest of the procedure:

D1: WO 99/34826 A (IMP COLLEGE INNOVATIONS LTD ;KAY ANTHONY B (GB); LARCHE MARK (GB)) 15 July 1999 (1999-07-15)

D2: NIEDERBERGER VERENA ET AL: "Calcium-dependent immunoglobulin E recognition of the apo- and calcium-bound form of a cross-reactive two EF-hand timothy grass pollen allergen, Phl p 7." FASEB JOURNAL, vol. 13, no. 8, May 1999 (1999-05), pages 843-856, XP002221491 ISSN: 0892-6638

General Observations

This Authority has carefully considered the Applicant's response to the issued Written Opinion. However, the comments and objections relating to lack of unity and inventive step expressed in said Written Opinion are essentially unchanged - see below. In summary, the technical effects of the truncated/mutated pollen allergens disclosed in the description are not considered surprising in the light of the teachings of D1 and D2, which teach that reduced reactivity with IgE antibodies after making such modifications was to be expected.

IV) Unity

1) SEQ ID Nos: 2 and 3 correspond to essentially different parts of Phl p 7, whilst SEQ ID Nos: 4-6 are full length and share one mutation in common.

Consequently, at least three separate inventions are present in the claims (or more if the mutation shared between SEQ ID Nos: 4-6 does not provide a surprising technical effect - see section V below), these being:

1) 2-EF hand allergen fragments corresponding to SEQ ID No: 2
2) 2-EF hand allergen fragments corresponding to SEQ ID No: 3
3) 2-EF hand allergen mutants with at least one mutation in common corresponding to SEQ ID No: 4 (e.g. SEQ ID Nos: 5 and 6)

2) In view of the fact that the approaches of truncating and mutating 2-EF hand allergens to reduce allergenicity were already known from D1 and D2, there is no technical relationship between the features of each of the above inventions that defines a contribution over the prior art.

3) However, in order to expedite the procedure and since all aspects of the application can be examined by this authority without significant extra effort, the Applicant has not been invited to pay additional examination fees at this time.

V) Novelty, inventive step and industrial applicability

Inventive step

1) The present application does not satisfy the criterion set forth in **Article 33 (3) PCT** because the subject-matter of **claims 1-15** does not involve an inventive step (**Rule 65.1 and 65.2 PCT**).

2) The present application is directed to pollen allergen fragments and/or mutants that have reduced IgE binding activity and are therefore less allergenic and more suitable for specific immunotherapy.

3) The general inventive concept of truncating allergens such as Phl p 7 in order to make them less allergenic is already disclosed in D1 (see page 9, lines 9-14 and page 66, lines 17-19).

Furthermore, D2 states:
"The fact that patients exhibited reduced IgE binding to certain Phl p 7 conformations may represent a basis for the generation of "hypoallergenic" allergen variants for specific immunotherapy. The latter concept has been used to generate recombinant fragments and mutants of the major birch pollen allergen Bet v 1 with reduced anaphylactic activity. Similar results may be obtained if the calcium binding sites of Phl p 7 are destroyed by site-directed mutagenesis" (emphasis added).

4) In view of D1 and D2, the general concept of truncating or mutating (particularly in the EF hand regions) the Phl p 7 allergen in order to make it less allergenic (particularly to reduce reactivity with IgE) was known. Consequently, the subject-matter of **claims 1-15** cannot be considered inventive in the light of D1 and D2 taken alone or in combination.